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PATENT SPECIFICATION

DRAWINGS ATTACHED

873,935

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Improvements in and relating to new isoquinoline phthalides and their process of preparation.

COMPLETE SPECIFICATION

I, MAURICE JEANSON, a citizen of the French Republic, of 68, Boulevard de Courcelles, Paris (Seine), France, do hereby declare the invention, for which I pray that a patent may be granted to me, and the method by which it is to be performed, to be particularly described in and by the following statement:

The present invention relates to new industrial products, namely isoquinoline phthalides (I) having the general formula shown in Fig. 1 of the accompanying drawing in which R_1, R_2 and R_3 are identical or different alkyl radicals and X is hydrogen or a nitro, or amino group, and their acid addition salts.

According to the usual nomenclature, the compounds I of the invention are thus 2-methyl-6.7-methylenedioxy - 8 - methoxy-1-[4.5.6-Trialkyl-phthalidyl-(3)]-1.2.3.4 - tetrahydroisoquinolines, their derivatives substituted at position 7 on the phthalidyl portion and their acid addition salts.

These compounds comprise an asymmetric carbon atom at position 3 of the phthalidyl portion and the invention also relates to the racemic compounds obtained in the course of the synthesis and the optically active products obtained by resolution of the racemic compounds according to conventional methods.

The new compounds I are very active as inhibitors of histidine-decarboxylase while having a very low toxicity. They can therefore be used in all applications where this inhibition is desirable for example in the food industries and for the stabilization of preserved food. Further, they are of a great therapeutic interest and permit lowering histaminemia by acting against allergic ailments. They are also antinausea products which can be used against sea and air sickness.

Another object of the invention is to provide a process of preparing the new compounds I. This process comprises condensing cotarnine with a phthalide (II) having the general formula shown in Fig. 2, in which X, R_1, R_2 and R_3 have the aforementioned significations.

The condensation is advantageously carried out in a solvent such as alcohol by refluxing. It can be effected with or without a dehydrating agent such as sodium carbonate or sodium sulphate. This condensation is effected most easily when in the phthalide (II) X is a NO_2 group, so that there is often advantage in using such a phthalide in the condensation even when it is desired to obtain a compound I in which X has a signification other than NO_2. Indeed, it suffices in this case to convert the NO_2 group into the desired X group once the condensation has been obtained. The NO_2 group can thus be converted into an amino group by reduction and the latter into a hydrogen atom through the diazonium derivative in accordance with the Sandmeyer-Gattermann method.

The majority of the phthalides (II) are new compounds. This is particularly so for all the phthalides (II) in which R_1, R_2 and R_3 each have at least two carbon atoms.

The phthalide (II) is itself prepared from the corresponding trialkoxyl benzoic acid by condensation with formaldehyde followed preferably by introduction of a nitro group as substituent X for the above-mentioned reason.

The condensation with formaldehyde is preferably effected in the presence of hydrochloric acid to which is added, if desired, acetic acid.

The following examples illustrate the invention, it being understood that the scope of the latter is in no way limited thereto.

EXAMPLE 1.

2-Methyl-6.7-methylenedioxy - 8 - methoxy-1-[4.5.6-triethoxy-7-nitro-phthalidyl - (3)]-1.2.3.4-tetrahydroisoquinoline.

(Compound 1, $R_1=R_2=R_3= -C_2H_5$, $X= -NO_2$).

a) 4.5.6.-Triethoxy-phthalide.

A mixture of 3.4.5-triethoxy-benzoic acid (3 kgs), 40% formaldehyde (7,500 cc) and concentrated hydrochloric acid (3,600 cc) is refluxed for 3 hours. Upon cooling, the product sets into a solid. It is diluted and filtered. The precipitate is recrystallized in ethanol. The product melts at 127°C. It is in the form of white silky needles, very slightly soluble in water, soluble when hot in ethanol and ethylic ether, and very soluble in chloroform.

C%	calculated	63.15	
	found	63.18	63 13
H%	calculated	6.76	
	found	6.86	6.95

b) 4.5.6.-Triethoxy-7-nitro-phthalide.

To a luke-warm solution of 600 g of 3.4.5-triethoxy-phthalide in 1500 cc of crystallizable acetic acid there are slowly added 1500 cc of nitric acid (d=1.49) with continuous agitation. The temperature is maintained between 30° and 40°C. The addition lasts several days. The mixture is diluted and the precipitate which separates out is recrystallized in alcohol. The nitro derivative obtained melts at 92°C and is in the form of large crystals which become slowly coloured on exposure to light. It is insoluble in water, soluble hot ethanol and ethyl ether, and very soluble in chloroform.

C%	calculated	54.02	
	found	54.05	53.95
H%	calculated	5.46	
	found	5.91	5.75
N%	calculated	4.50	
	found	4.06	4.20

c) Condensation with cotarnine.

There are dissolved in 4 litres of absolute ethyl alcohol 400 g of 4.5.6-triethoxy-7-nitro-phthalide and 300 g of cotarnine base. 300 g of anhydrous sodium sulphate are added and the mixture is heated to a slow boil for 2 to 3 days in a nitrogen atmosphere. The sodium sulphate is filtered hot and left in an icebox for two days. The product is in the form of yellowish crystals melting at 150°C. It is insoluble in water, fairly soluble in boiling alcohol, and very soluble in chloroform.

N%	calculated	5.28
	found	5.35 and 5.42

EXAMPLE 2.

2-Methyl-6.7-methylenedioxy - 8-methoxy-1-[4.5.6-triethoxy - 7 - amino-phthalidyl-(3)]-1.2.3.4.-tetrahydroisoquinoline.

(Compound (I), $R_1=R_2=R_3=C_2H_5$, $X=NH_2$).

There is added slowly while cooling with running water a solution of 350 g of stannous chloride in 400 cc of concentrated hydrochloric acid in a solution of 130 g of nitro derivative (obtained in accordance with Example 1) in 600 cc of crystallizable acetic acid. The mixture is left for 2 to 3 days in an icebox. Thereafter it is poured slowly into 8 litres of water while vigorously agitating so as to prevent formation of lumps. The double salt of SnU_2 and the amino derivative precipitates in the form of a flocculent white precipitate. Thereafter a large excess of soda lye is added to destroy the complex and liberate the amino derivative. The addition is slow and the cooling energetic so as to avoid hydrolysis of the product. The product is extracted with chloroform, dried and distilled. When the major part of the chloroform has been evaporated, boiling methyl alcohol is added and the mixture is allowed to cool. The amino derivative crystallizes in the form of magnificent white needles. It melts at 183°C. It is soluble in chloroform and ethanol, insoluble in water; and slightly soluble in water acidified by mineral acids

C%	calculated	62.4	
	found	62.27	62.25
H%	calculated	6.4	
	found	6.87	6.68
N%	calculated	5.6	
	found	5.75	5.93

EXAMPLE 3.

2-Methyl-6.7-methylenedioxy - 8 - methoxy-1 - [4.5.6.-triethoxy-phthalidyl(3)] - 1.2.3.4-tetrahydroisoquinoline.

(Compound I, $R_1=R_2=R_3= -C_2H_5$, $X=H$).

80 g of amino derivative (obtained in accordance with Example 2) are dissolved in a mixture of 400 cc of water and 250 cc of concentrated HCl. The mixture is cooled at 0°C and a solution of 25 g of sodium nitrite in a little water is slowly added. The mixture is left for one hour in an icebox and then 300 cc of 50% hypophosphorous acid are slowly poured in during one hour. After leaving the mixture for 24 to 48 hours in an icebox it is diluted and alkalinized with ammonia. The mixture is extracted with chloroform, dried and distilled. When nearly all the chloroform has evaporated, boiling methanol is added and the mixture allowed to cool. The product crystallizes in the form of yellowish needles melting at 183°C. Upon recrystallization in alcohol and decolourizing with animal-black, there is obtained an almost white product which melts at 185°C. It is insoluble in water, soluble in boiling ethyl alcohol and very soluble in chloroform.

C%	calculated	64.32	
	found	64.42	64.55
H%	calculated	6.39	
	found	6.46	6.42
N%	calculated	2.88	
	found	3.09	2.98

EXAMPLE 4.

2-Methyl-6.7-methylenedioxy - 8 - methoxy-1-[4.5.6.-trimethoxy-7-nitro-phthalidyl - (3)]-1.2.3.4-tetrahydroisoquinoline.

(Compound I, $R_1=R_2=R_3=$ $-CH_3$, $X=NO_2$).

a) 4.5.6.-trimethoxy-phthalide.

This compound is known. It can furthermore be prepared as described in Example 1 for the 4.5.6-triethoxy derivative by replacing the 3.4.5-triethoxy-benzoic acid by 3.4.5-trimethoxy-benzoic acid.

b) 4.5.6-trimethoxy-7-nitro-phthalide.

The trimethoxyphthalide is nitrated with nitric acid (D=1.49) in acetic acid. It is diluted and the precipitate is recrystallized in ethanol. The nitro derivative melts at 115°C. It is insoluble in water and very soluble in chloroform.

N%	calculated	5.20	
	found	5.32	5.30

c) Condensation with cotarnine.

Equimolecular quantities of nitro-phthalide and cotarnine base are condensed in ethylic alcohol. After 10 minutes of heating, the condensation product precipitates. The mixture is heated a further two hours and allowed to cool. The precipitate is filtered, washed with alcohol and dried. It melts at 192°C and is in the form of a yellowish microcrystalline powder, insoluble in water, very slightly soluble in alcohol even when hot and soluble in chloroform.

N%	calculated	5.73	
	found	5.82	5.91

EXAMPLE 5.

2-Methyl-6.7-methylenedioxy - 8 - methoxy-1-[4.5.6-trimethoxy - 7 - amino-phthalidyl-(3)]-1.2.3.4-tetrahydroisoquinoline.

(Compound I, $R_1=R_2=R_3=$ $-CH_3$, $X=NH_2$).

50 g of the nitro derivative (obtained in accordance with Example 4) are dissolved in 250 cc of glacial acetic acid. A little tin shot and a solution of 120 g of stannous chloride in 120 cc of concentrated hydrochloric acid are added, taking care that the temperature does not exceed 15°C. The mixture is left 6 hours and then diluted with 2 litres of water. An excess of soda lye is poured in slowly while agitating and cooling. The mixture is extracted with chloroform, dried and distilled. When nearly all the chloroform has evaporated, boiling methyl alcohol is added. The amino product crystallizes in the form of fine white needles. It is insoluble in water, slightly soluble in alcohol and soluble in chloroform. M.P.=193°C.

C%	calculated	60.26	
	found	60.03	60.24
H%	calculated	5.67	
	found	6.13	5.85
N%	calculated	6.11	
	found	6.08	5.90

EXAMPLE 6.

2-Methyl-6.7-methylenedioxy - 8 - meth xy-1-[4.5.6-trimethoxy-phthalidyl-(3)] - 1.2.3.4-tetrahydroisoquinoline.

(Compound I, $R_1=R_2=R_3=$ $-CH_3$, X=H).

This compound is obtained by de-amination by means of hypophosphorus acid of the amino derivative obtained in accordance with Example 5. The procedure is exactly the same as that described in Example 3. There are obtained yellowish needles melting at 187°C, insoluble in water, very slightly soluble in alcohol and soluble in chloroform.

C%	calculated	62.1	
	found	62.4	62.45
H%	calculated	6.64	
	found	6.18	6.30
N%	calculated	3.16	
	found	3.57	3.35

The scope of the invention is not intended to be limited to the Examples described hereinbefore.

WHAT I CLAIM IS:

1. As new compounds: isoquinoline phthalides having the general formula shown in Fig. 1 of the accompanying drawing, in which R_1, R_2 and R_3 are identical or different alkyl radicals, and X is hydrogen or nitro or amino group, and their acid addition salts.

2. 2-Methyl - 6.7 - methylenedioxy - 8 - methoxy-1 - [4.5.6-triethoxy-phthalidyl-(3)]-1.2.3.4-tetrahydroisoquinoline and the derivatives substituted at position 7 on the phthalidyl portion by the nitro and amino groups.

3. 2-Methyl - 6.7 - methylenedioxy - 8 - methoxy - 1 - [4.5.6-trimethoxy-phthalidyl-(3)]-1.2.3.4-tetrahydroisoquinoline and its derivatives substituted at position 7 on the phthalidyl portion by the nitro and amino groups.

4. Process of preparing the compounds according to claim 1, comprising condensing cotarnine with a phthalide having the general formula shown in Fig. 2 of the accompanying drawing, wherein X, R_1, R_2 and R_3 have the aforementioned significations.

5. Process as claimed in claim 4, wherein the condensation is effected by refluxing in a solvent, such as alcohol.

6. Process as claimed in claim 4 or 5, wherein the condensation is effected in the presence of a dehydrating agent such as sodium carbonate or sulphate.

7. Process as claimed in any one of the claims 4 to 6, wherein the phthalide condensed with cotarnine comprises as substi-

tuent X a nitro group, said nitro group being converted after condensation into an amino group and thereafter into a hydrogen atom, if isoquinoline phthalides are to b btained in which X is other than a nitro group.

8. Process as claimed in any one of the claims 4 to 6, wherein the phthalide to be condensed with the cotarnine is itself prepared from the corresponding trialkoxyl benzoic acid by condensation with formaldehyde, followed preferably by introduction of a nitro group as substituent X.

9. Process as claimed in claim 8, wherein the condensation with formaldehyde is effected in the presence of hydrochloric acid to which is added, if desired, acetic acid.

10. Process of preparing the compounds according to claim 1, substantially as described with reference to the Examples.

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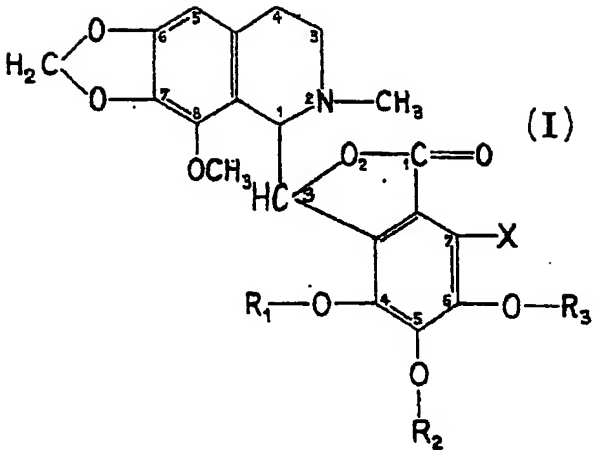
873,935 COMPLETE SPECIFICATION
1 SHEET

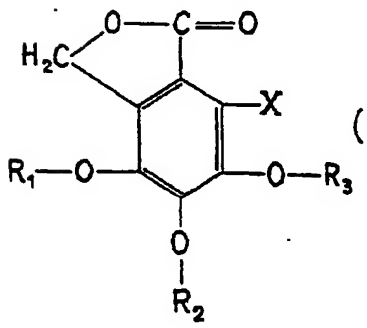
This drawing is a reproduction of the Original on a reduced scale.

Fig. 1



(I)

Fig. 2



(II)